amendments can be found throughout the specification of the present application. For example of the support, see pages 2-3, page 6, lines 17-23, and page 17, line 14 to page 18, line 12.

Applicants believe that the instant amendments place the specification in full compliance with the sequence identification rules including the requirements of Rule 37 C.F.R. 1.821(d).

Claims 1-3 have been rejected under 35 U.S.C. §101 because the claimed invention allegedly is directed to non-statutory subject matter.

Applicants believe that the claims as amended are fully compliant with the statutory subject matter requirements of 35 U.S.C. §101. Applicants request that the Examiner withdraw the rejection and reconsider the claims.

Claims 7 and 8 have been rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7 and 8 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because it is unclear how they further limit the compositions of claim 6.

Claims 1-3 and 6-8 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification; as allegedly non-enabling for proteins other than SEQ ID NO 2 and 4; and as allegedly being so broad as to encompase any protein capable of activating transcription factor NF-κB.

The specification and claims, as amended, are fully compliant with all of the requirements of 35 U.S.C. §112, including §112, first paragraph and §112, second paragraph. Applicants request that the Examiner withdraw the rejections and reconsider the claims.

The Office Action notes that claims 1-3 and 6-8 are rejected under 35 U.S.C.112, first paragraph, as containing subject matter which was not described in the specification in such a way to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant respectfully submits that the present application after the above amendment fully satisfies the requirements of Section 112, including the "enabling any person skilled in the art to which pertains" requirements of Section 112, first paragraph.

Any person skilled in the relevant art can make and use the instant invention by reference to the specification, including the Sequence Listing, the suppression subtractive hybridization technique (see, page 5, line 16 to page 7, line 7), the reporter gene assay (see, page 9, line 19 to page 10, line 13), the *in vitro* kinase assay (see, page 10, line 17 to page 11, line 23), the immunoprecipitation procedure (see, page 13, line 23 to page 14, line 16).

New claims 11 and 12 distinctly point out the second invention of the present application as a pharmaceutical composition which comprises peptide having IκB kinase activity and I-TRAF binding activity. Therefore, the claims 11 and 12 after amendment are definite in the recitation of "which acts on the immune response mechanism" and "which is a preventive or therapeutic agent for diseases involving the I-TRAF or the TRAF molecule".

Claims 1-3 were rejected under 35 U.S.C. §102(a) as being allegedly anticipated by Shimada, et al.

Applicant respectfully submits that the present application fully satisfies the patentability for Section 102(a) despite the disclosure by Shimada. Since the journal paper "IKK-i, a novel lipopolysaccharide-inducible kinase that is related to IκB kinases" Shimada et al., 1999, International Immunology, Vol.11, No.8, pp.1357-1362, which is authored by the inventors of the present application, was published in 1999 after the priory application (JP 10-

304085) filed on October 26, 1998. A copy of an English language translation of the JP 10-304085 document is filed herewith.

Claims 1-3 were rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Nagase, et al. (EMBL entry D63485) as evidenced by Cao (US Patent 5,776,717).

Applicant respectfully submits that the present application fully satisfies the patentability for Section 102(b) despite the disclosure by Nagase et al. and US Patent 5,776,717. Although the DNA sequence of human gene KIAA0151 was disclosed by Nagase et al., the cited document did not isolate the peptide encoded by this sequence, did not suggest that the amino acid sequence would be SEQ ID NO:2, and did not reveal physiological function of the peptide.

The disclosure of Cao fails to provide evidence overcoming the limitations of the disclosure of Nagase. *Cao had made a misunderstanding to identify another human gene as KIAA0151 human gene.* As the Cao reference is understood, the specification of Cao teaches that the amino acid sequence of *"SEQ ID NO:2 which distinguishes both the KIAA0151 gene product and the translation product of SEQ ID NO:1" (column 2 lines 14-15).*

Applicants respectfully submit that the We will show you that the amino acid sequence SEQ ID NO:2 (Cao) is substantially different from the amino acid sequence of KIAA0151 gene product. ***As can be seen from amino acid sequence alignment result which is attached hereto, the sequence of US Patent 5,776,717 shows only 48% identity to the sequence of the KIAA0151 gene product.*** In this alignment analysis, "Query" shows the amino acid sequence of SEQ ID NO:2 (Cao) in the US Patent 5,776,717, and "Sbjet" shows corresponding amino acid sequence of KIAA0151 gene product.

Applicants further argue that the physiological function of the peptide recited by Cao and the peptide of SEQ IN NO 2 of the present invention are completely different. Cao recites "a family of IκB kinases including a TRAF2-associated kinase activity (designated T2K) and

phosphorylates the IKB molecules on the specific regulatory serine residues" (See column 1 lines 36-40).

In contrast, the present invention provides "An isolated and purified protein having IκB kinase activity, I-***TRAF binding activity*** and ability to activate NF-κB".

As suggested in the journal document "I-TRAF is a novel TRAF-interacting protein that regulates TRAF-mediated signal transduction" Rothe et al.(Tularik, Inc.), 1996, Proc.Natl.Acad.Sci.USA, Vol.93, pp.8241-8246, which is attached hereto, I-TRAF may be a natural inhibitor of TRAF function (page 8246 left column lines 1-14). Applicants argue that I-TRAF is an inhibitor of TRAFs and it shall be separately classified from TRAF1 and TRAF2.

Claim 9 is patentable over the disclosure of Nagase as evidenced by Cao. Claims 10-12 depend from claim 9 and are therefore also patentable over Nagase as evidenced by Cao.

Claims 6-8 were rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Shimada, et al. in view of Mercurio et al.

As discussed *supra*, Shimada was published in 1999 after the priority application (JP 10-304085) filed on October 26, 1998. Thus the rejection under 35 U.S.C. §103(a) as being unpatentable over Shimada in view of Mercurio is simply not proper. Applicants request that the rejection be withdrawn.

Claims 6-8 were rejected under 35 U.S.C. §103(a) as being allegedly anticipated by Nagase, et al. (EMBL entry D63485) in view of Cao and Mercurio et al. The rejection is traversed.

Nagase et al. did not reveal physiological function of KIAA0151 gene product. Moreover, Nagase failed to identify the peptide amino acid sequence encoded by KIAA0151 and

further failed to isolate the peptide encoded by KIAA0151. Cao appears to have mis-identified the peptide expressed by another human gene sequence with the peptide encoded by KIAA0151 human gene.

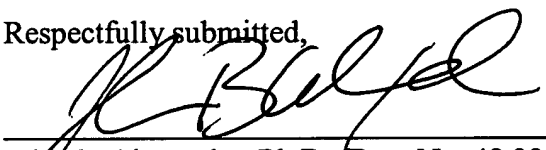
Mercurio fails to overcome the limitations of any combination of Nagase and Cao to teach or suggest an isolated and purified peptide selected from SEQ ID NO:2, SEQ ID NO:4, or a polypeptide having at least 82% homology with SEQ ID NO:2.

The discloaure of Mercurio is insufficient to overcome the limitations of Nagase evidenced by Cao. As the reference is understood, Mercurio neither discloses nor suggests that IκB kinase has I-TRAF binding activity. Thus no combination of Nagase, Cao and/or Mercurio disclose or suggest any pharmaceutical composition comprising IKK-i protein having I-TRAF binding activity and the present invention would not have been obvious to one skilled in the art based on any combination of the cited documents.

Claim 9 would not have been obvious to one skilled in the art from any combination of Nagase, Cao and/or Mercurio. Claims 10-12 depend from claim 9 and are therefore also patentable over any combination of Nagase, Cao and/or Mercurio.

Early consideration and allowance of the application are earnestly solicited.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES TO CLAIMS

Please note that additions to the claims are shown underlined and deletions are shown in brackets.

IN THE SPECIFICATION:

Kindly amend the Brief Description of Drawings, starting at page 3, line 18, as follows:

Fig. 3 shows a comparison of the amino acid sequences of human IKK-i (SEQ. ID NO 2) and mouse IKK-i (SEQ. ID NO 4). In the figure, the part enclosed by a rectangle shows an identical sequence; a part [] shows a kinase domain; and * shows a leucine-zipper domain;

Fig. 4 shows a comparison of the amino acid sequences of IKK-i (SEQ. ID NO 2), and amino acid sequences which comprise insertions or deletions in the SEQ. ID NO 2 amino acid sequence, i.e., IKK-α, IKK-β. The parts colored with a gray backgrounds in the figure show identical sequences; the part [] shows a kinase domain; the part enclosed by a rectangle shows an activation loop; and * mark shows an amino acid residue which may be important for kinase activity.

IN THE CLAIMS:

Please cancel claims 1-3 and 6-8, without prejudice or disclaimer.

Kindly add new claims 9-12, as follows:

9. (new) An isolated and purified protein having IκB kinase activity, I-TRAF binding activity and ability to activate NF-κB, wherein said protein is selected from the group consisting of:

(a) the protein having the amino acid sequence of SEQ ID NO:2

(b) the protein having the amino acid sequence of SEQ ID NO:4, and

(c) a polypeptide which is more than 82% homologous with the polypeptide having the amino acid sequence of SEQ ID NO:2

10. (new) A pharmaceutical composition comprising the protein according to claim 9 and pharmaceutically acceptable carrier.

11. (new) The pharmaceutical composition according to claim 10, which acts on the immune response mechanism.

12. (new) The pharmaceutical composition according to claim 12, which is a preventive or therapeutic agent for diseases involving the I-TRAF or the TRAF molecule.

part of #14

>gi|7661946|ref|NP_054721.1| (NM_014002) IKK-related kinase epsilon [Homo sapiens]
gi|14548079|sp|Q14164|IKKE_HUMAN Inhibitor of nuclear factor kappa-B kinase epsilon subunit kappa-B kinase epsilon) (IkBKE) (IKK-epsilon) (IKK-E) (Inducible I kappa-B kinase) (IKK-i)
gi|1469884|dbj|BAA09772.1| (D63485) The KIAA0151 gene product is classified into serine/threonine kinase. [Homo sapiens]
gi|6012176|dbj|BAA85155.1| (AB016590) inducible IkappaB kinase [Homo sapiens]
gi|7288878|gb|AAF45307.1|AF241789_1 (AF241789) IKK epsilon [Homo sapiens]
Length = 716

Score = 666 bits (1719), Expect = 0.0
Identities = 351/717 (48%), Positives = 464/717 (63%), Gaps = 15/717 (2%)

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Query: 1   MQSTSNHLWLLSDILGQGATANVFRGRHKKTGDLFAIKVFNNISFLRPVDVQMREFEVLK 60
           MQST+N+LW   D+LGQGATA+V++ R+KK+G+L A+KVFN  S+LRP +VQ+REFEVL+
Sbjct: 1   MQSTANYLWHTDDLLGQGATASVYKARNKKSGELVAVKVFNTTSYLRPREVQVREFEVLR 60

Query: 61  KLNHKNIVKLFAIEEETTTRHKVLIMEFCPCGSLYTVLEEPSNAYGLPESEFLIVLRDVV 120
           KLNH+NIVKLFA+EE    +R KVL+ME+C  GSL +VLE P NA+GLPE EFL+VLR VV
Sbjct: 61  KLNHQNIVKLFAVEETGGSRQKVLVMEYCSSGSLLSVLESPENAFGLPEDEFLVVLRCVV 120

Query: 121 GGMNHLRENGIVHRDIKPGNIMRVIGEDGQSVYKLTDFGAARELEDDEQFVSLYGTEEYL 180
           GMNHLRENGIVHRDIKPGNIMR++GE+GQS+YKLTDFGAAREL+DDE+FVS+YGTEEYL
Sbjct: 121 AGMNHLRENGIVHRDIKPGNIMRLVGEEGQSIYKLTDFGAARELDDDEKFVSVYGTEEYL 180

Query: 181 HPDMYERAVLRKDHQKKYGATVDLWSIGVTFYHAATGSLPFRPFEGPRRNKEVMYKIITG 240
           HPDMYERAVLRK  QK +G TVDLWSIGVT YHAATGSLPF PF GPRRNKE+MY+I T
Sbjct: 181 HPDMYERAVLRKPQQKAFGVTVDLWSIGVTLYHAATGSLPFIPFGGPRRNKEIMYRITTE 240

Query: 241 KPSGAISGVQKAENGPIDWSGDMPVSCSLSRGLQVLLTPVLANILEADQEKCWGFDQFFA 300
           KP+GAI+G Q+ ENGP++WS  +P++C LS GLQ  L P+LANILE +Q KCWGFDQFFA
Sbjct: 241 KPAGAIAGAQRRENGPLEWSYTLPITCQLSLGLQSQLVPILANILEVEQAKCWGFDQFFA 300

Query: 301 ETSDILHRMVIHVFSLQQMTAHKIYIHSYNTATIFHELVYKQTKIISSNQELIYEGRRLV 360
           ETSDIL R+V+HVFSL Q   H IYIH++NT  IF E V+KQT +   +QE ++EG   V
Sbjct: 301 ETSDILQRVVVHVFSLSQAVLHHIYIHAHNTIAIFQEAVHKQTSVAPRHQEYLFEGHLCV 360

Query: 361 LEPGRLAQHFPKTTEENPIFVVSREPLNTIGLIYEKISLPKVHPRYDLDGDASMAKAITG 420
           LEP   AQH   TT  +P+ + S      +      + +PK  P+ DL  D + AK + G
Sbjct: 361 LEPSVSAQHIAHTTASSPLTLFSTAIPKGLAFRDPALDVPKFVPKVDLQADYNTAKGVLG 420

Query: 421 VVCYACRIASTLLLYQELMRKGIRWLIELIKDDYNETVHKKTEVVITLDFCIRNIEKTVK 480
               A R+A  LL  QELM +G+ W++E+++      T  +  EV  T    + +  T
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Query: 481 VYEKLMKI--NLEAAELGEISDIHTKLLRLSSSQGTIETSLQDIDSRLSPGGSLADAWAH 538
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Query: 539 QEGTHPKDRNVEKLQVLLNCMTEIYYQFKKDKAERRLAYNEEQIHKFDKQKLYYHATKAM 598
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Sbjct: 530 SRDQVHEDRSIQQIQCCLDKMNFIYKQFKKSRMRPGLGYNEEQIHKLDKVNFSHLAKRLL 589

Query: 599 THFTDECVKKYEAFLNKSEEWIRKMLHLRKQLLSLTNQCFDIEEEVSKYQEYTNELQETL 658
           F +ECV+KY+A L    + +R +   R  L +          E    QE  ++L E L
Sbjct: 590 QVFQEECVQKYQASLVTHGKRMRVVHETRNHLRLVGCSVAACNTEAQGVQESLSKLLEEL 649

Query: 659 PQKMFT--ASSGIKHTMTPIYPSSNTLVEMTLGMKKLKEEMEGVVKELAENNHILER 713
           ++    A              S T  ++ L M++L E M+ +  +L +NN I+ER
Sbjct: 650 SHQLLQDRAKGAQASPPPIAPYPSPTRKDLLLHMQELCEGMKLLASDLLDNNRIIER 706
```

Query = SEQ ID NO:2 in the USP 5,776,717

Sbjct = KIAA0151 gene product = human IKK-i

```
>gi|7661946|ref|NP_054721.1|  (NM_014002) IKK-related kinase epsilon [Homo sapiens]
 gi|14548079|sp|Q14164|IKKE_HUMAN  Inhibitor of nuclear factor kappa-B kinase epsilon subunit
           kappa-B kinase epsilon) (IkBKE) (IKK-epsilon) (IKK-E)
           (Inducible I kappa-B kinase) (IKK-i)
 gi|1469884|dbj|BAA09772.1|  (D63485) The KIAA0151 gene product is classified into
           serine/threonine kinase. [Homo sapiens]
 gi|6012176|dbj|BAA85155.1|  (AB016590) inducible IkappaB kinase [Homo sapiens]
 gi|7288878|gb|AAF45307.1|AF241789_1  (AF241789) IKK epsilon [Homo sapiens]
          Length = 716

 Score =  666 bits (1719), Expect = 0.0
 Identities = 351/717 (48%), Positives = 464/717 (63%), Gaps = 15/717 (2%)

Query: 1   MQSTSNHLWLLSDILGQGATANVFRGRHKKTGDLFAIKVFNNISFLRPVDVQMREFEVLK 60
            MQST+N+LW    D+LGQGATA+V++ R+KK+G+L A+KVFN  S+LRP +VQ+REFEVL+
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Query: 361 LEPGRLAQHFPKTTEENPIFVVSREPLNTIGLIYEKISLPKVHPRYDLDGDASMAKAITG 420
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Sbjct: 421 AGYQALRLARALLDGQELMFRGLHWVMEVLQ----ATCRRTLEVARTSLLYLSSSLGT-- 474

Query: 481 VYEKLMKI--NLEAAELGEISDIHTKLLRLSSSQGTIETSLQDIDSRLSPGGSLADAWAH 538
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                  +DR+++++Q  L+  M   IY QFKK +     L YNEEQIHK DK     + A + +
Sbjct: 530 SRDQVHEDRSIQQIQCCLDKMNFIYKQFKKSRMRPGLGYNEEQIHKLDKVNFSHLAKRLL 589

Query: 599 THFTDECVKKYEAFLNKSEEWIRKMLHLRKQLLSLTNQCFDIEEEVSKYQEYTNELQETL 658
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